AUCTORES
Globalize your Research

Journal of Cancer Research and Cellular Therapeutics

Tahereh Kalantari *

Open Access

Review Article

Molecular Progression and Multiple-Target Biomarkers in Multiple Myeloma: A Brief Review

Amin Hasanpour [1], Tahereh Kalantari [1,2] *

[1] Division of hematology and blood banking, Department of Medical Laboratory Sciences, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

[2] Diagnostic Laboratory Sciences and Technology Research Center, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

***Corresponding Author:** Tahereh Kalantari, Department of Laboratory Sciences, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.

Received Date: November 30, 2023; **Accepted Date:** December 11, 2023; **Published Date:** December 19, 2023

Citation: Amin Hasanpour, Tahereh Kalantari, (2023), Molecular Progression and Multiple-Target Biomarkers in Multiple Myeloma: A Brief Review, *J. Cancer Research and Cellular Therapeutics*, 7(6); **DOI:**10.31579/2640-1053/170

Abstract

Multiple myeloma (MM) is a type of cancer that affects the plasma cells in your bone marrow. The severity of the disease can range from a less serious condition called monoclonal gammopathy of unknown significance (MGUS) to a more severe form called plasma cell leukemia (PCL). To ensure early treatment, the International Myeloma Working Group (IMWG) has updated the criteria for when to begin therapy. In this article, we discuss how MM progresses from MGUS to full-blown cancer at a molecular level. We also explain that because the disease is so complex, it cannot be treated with a single approach or by targeting one specific biomarker. While traditional biomarkers can be helpful in tracking the severity of the cancer, new biomarkers are being developed to create multi-target therapies that can be used at different stages of the disease.

Keywords: multiple myeloma (MM); MGUS; SMM; genetics; established and novel biomarkers

Introduction

Multiple myeloma (MM) is a complex type of blood cancer that has its roots in a condition called monoclonal gammopathy of uncertain significance (MGUS). MGUS is often discovered by chance, particularly in older adults, and can be seen as a warning sign for the eventual development of multiple myeloma [1]. The transition from a symptomless precursor to an obvious illness occurs slowly, at a rate of approximately 1% per annum. This highlights a path characterized by complex interactions between genetics and the environment [2].

In the context of MM, there is a very important chapter that discusses asymptomatic or smoldering myeloma (SMM). This is a condition that makes up a significant portion of newly diagnosed MM cases [3]. At this stage, it can be compared to standing at a crossroads where certain medical markers indicate that something is happening, but the usual dramatic symptoms of advanced MM are not present. From a clinical perspective, it is somewhat of a mystery, as the risk of progressing to more severe stages can vary, and it requires close monitoring and attention over time [4].

The emergence of advanced genomic and proteomic technologies has revealed a world of chromosomal abnormalities and molecular events that play significant roles in the progression of MM patients [5]. Medical researchers have recently identified a mix of biomarkers, some genomic and some non-genomic, that are improving our ability to diagnose and predict outcomes [6].

The International Myeloma Working Group (IMWG) made a major development in 2014 by redefining the diagnostic criteria for MM. This included advanced biomarkers that can indicate a greater risk of disease progression [7]. This development has opened up new possibilities for early intervention, which has the potential to change the course of the disease for many patients.

The goal of this paper is to navigate the complex progression of MM, from its initial stages of MGUS and SMM to its more severe forms. We will examine the intricate molecular mechanisms of myeloma genesis, investigate the influence of new biomarkers on disease categorization, and consider how these advancements alter our approach to treatment. [8].

Multiple Myeloma (MM)

MM**,** also known as myeloma**,** is a type of cancer that affects plasma cells and has a wide range of clinical and genetic variations. It is always preceded by a pre-malignant stage, often not given much attention. This pre-malignant stage is usually detected incidentally and is known as

monoclonal gammopathy of undetermined significance (MGUS). MGUS is more common in older people but only progresses to MM at a rate of around 1% per year. Patients with MGUS have a low level of monoclonal protein and abnormal plasma cells in the bone marrow but no indicators of active disease [1]. Approximately 14% of newly diagnosed myeloma patients are asymptomatic or smoldering myeloma (SMM) [2]. Asymptomatic or SMM is a condition where either the level of plasma cells in the blood is above 10%, or the monoclonal protein level is above 30 g/l. However, it does not show any of the clinical end-organ damage criteria that are used to define symptomatic multiple myeloma, such as CRAB (hypercalcemia, renal impairment, anemia, bone disease) [3]. SMM can be categorized into three distinct possibilities, namely MGUS with a higher but stable number of abnormal plasma cells, minimally progressive myeloma without CRAB criteria or myeloma-defining events, and moderately progressive myeloma with no damage to red blood cells, kidneys, or bones. For patients with standard-risk SMM, the risk of progression to active myeloma is 10% per year for the first five years, 3% per year for the next five years, and 1-2% per year for the next 10 years [4]. Efforts have been made to identify biomarkers that can predict the risk of progression for both MGUS and SMM to symptomatic disease. However, there has been a lack of concordance and validation of biomarkers, particularly with regard to SMM [5]. In 2014, The IMWG updated the definition of multiple myeloma with three new criteria for therapy initiation in addition to the CRAB criteria [6]. To diagnose multiple myeloma, three criteria must be met. These include a level of plasma cell infiltration greater than 60%, a serum-free light chain (sFLC) level/ratio greater than 100mg/l, and the presence of focal lesions on advanced imaging such as low dose whole body computerized tomography (CT), magnetic resonance imaging (MRI), and 18F fluorodeoxyglucose positron emission (18F FDG PET). In addition, the IMWG revised the definitions of renal disease and bone disease in the CRAB criteria and also defined a minimal plasma cell percentage infiltration in the bone marrow required to meet the definition of myeloma [6].

The molecular progression of MM from early to advanced stages

Myelomagenesis, the process of developing multiple myeloma (MM) [7], is initiated by molecular events such as chromosomal translocations and hyperdiploidy. Approximately 55% of MM patients exhibit recurrent chromosomal translocations involving the immunoglobin heavy chain (IgH) locus at 14q32 [8], with t (11;14) (q13; q32) and t (4;14) (p16; q32) being the most common [9]. Chromosomal hyperdiploidy is observed in up to 50% of MM patients and is characterized by a trisomy of the odd-numbered chromosomes [10]. These events lead to abnormal gene expression of the cyclin D family, which helps dormant cells grow [11].In monoclonal gammopathy of undetermined significance (MGUS), genetic abnormalities increase malignant plasma cells to >10% of bone marrow mononuclear cells. MM cells acquire non-synonymous point mutations in Ras family oncogenes involving APOBEC3B cytidine deaminase [8]. Moreover, c-Myc overexpression occurs exclusively in the progression of MGUS to MM [12]. Genomic instability due to DNA hypomethylation may accelerate disease progression [13]. In the terminal stage of myeloma, MM cells exhibit stroma-independent growth, forming extramedullary lesions, and leukemic conversion. This growth is sustained by the constitutive activation of Nuclear factor kappa B (NF-kB) [13]. The loss of genes encoding NF-kB pathway inhibitors and extensive structural abnormalities of chromosomes, such as complex translocations involving the c-Myc gene, duplication of chromosome 1q, and deletions of 1p32 or 17p13, are common in terminal-stage myeloma. TP53 mutations almost exclusively occur with 17p deletion, especially in refractory cases. TP53 mutations appear late in MM's clonal evolution and usually have oncogenic functions, including up-regulation of c-Myc and genes encoding proteasome subunits, which induce anti-cancer drug resistance [14,15].

Biomarkers: Their Importance in Multiple Myeloma Diagnosis and Therapy

1. *Established biomarkers*

To diagnose multiple myeloma, doctors use a series of biomarkers. These biomarkers can be divided into two types: nongenomic and genomic. Nongenomic biomarkers include the Durie-Salmon staging system (DSS) [15], the international staging system (ISS) [16], the revised ISS (RISS) [17], the percentage of plasma cells [18], chromosomal abnormalities [19], serum protein electrophoresis (SPE), urinary Bence-Jones protein [20], serum-free light chain (FLC) [21], and various imaging techniques such as metastatic skeletal survey (MSS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) with fluorodeoxyglucose (FDG) [22]. Genomic biomarkers include interphase fluorescence in situ hybridization (IFISH) [23] as a cytogenetic test and gene expression profiling (GEP) [24].

I. Nongenomic markers

The DSS was first reported in 1975 and is still used today as a diagnostic method for MM. However, it has certain limitations, such as the subjectivity involved in determining the extent of bone disease. As a result, another system for staging myeloma, ISS, was developed. The two most widely used staging systems in MM patients are the ISS and Durie–DSS [15]. However, both have limitations. For instance, the ISS prognostic model lacks biologic determinants of the disease. The ISS is a simple risk stratification system based on serum albumin and β2-microglobulin. Although it is powerful and reproducible, the outcome can be affected by serum albumin, which is a host factor and not disease-specific [16]. Furthermore, the ISS relies solely on tumor biological parameters and does not incorporate medical imaging modalities. The DSS, on the other hand, relies on clinical factors, such as the number of lytic bone lesions on a skeletal radiographic survey, serum calcium, level of hemoglobin, amount of M protein, and renal function. However, its classification based on the extent and number of bone lesions found by X-ray is observer-dependent, which makes it difficult to reproduce. To better stratify patients into homogenous survival groups, ISS was combined with serum lactate dehydrogenase (LDH) and chromosomal abnormalities to form a revised ISS (RISS) [18]. The RISS improves the prognostic value of the ISS by combining the variables in the ISS with the chromosomal abnormalities (CA) detected by IFISH (t(14;16), t(4;14), and del17p) [23] and serum LDH in those patients with newly diagnosed MM. According to recent studies, the RISS can also be used to stratify patients with relapsed/refractory MM [19]. When it comes to detecting MM, the use of both MRI and PET scans has become an important part of the diagnostic criteria [25]. In healthy individuals, the percentage of plasma cells is usually less than 3%, but this number can increase significantly in patients with MM, ranging from 10% to 100%, depending on the severity of the disease. Screening for plasma cell percentage is a common test performed to identify potential MM patients [26]. Monoclonal gammopathy is a type of cancer that occurs when a specific group of cancerous plasma cells produces a type of protein. These proteins, also called monoclonal or M proteins, can be detected using a test called serum protein electrophoresis (SPE), which shows a spike in the alpha, beta, or gamma globulin region. Detecting the presence of an M spike is important for monitoring the progression of the disease [27, 28].

Patients with monoclonal gammopathy may also have Bence Jones proteins in their urine, which are also known as kappa and lambda [29]. These proteins play a key role in diagnosing and predicting the prognosis of monoclonal gammopathy.

Elevated levels of immunoglobulin free light chain (FLC) [30] and an abnormal FLC ratio are common in monoclonal gammopathy and can affect the prognosis. An abnormal FLC ratio, where the involved and/or uninvolved FLC is ≥ 100, is now included in the updated diagnostic criteria for newly diagnosed monoclonal gammopathy [31].

II. Genomic markers

Multiple genetic abnormalities have been identified in patients suffering from MM. Hyperdiploidy and chromosome translocations are the most common of these genetic aberrations and are considered to be primary events. Studies have reported that IFISH and cytogenetics have prognostic significance. Specifically, t(14;16), t(14;20), and 17p deletion are associated with poor prognosis, while t(11;14), t(6;14), and Hyperdiploidy myeloma are associated with standard risk [32]. High-risk IFISH, such as t(4;14), t(14;16), and 17p deletion have been combined with ISS and lactate dehydrogenase to form the R-ISS for better prognostication. However, it is important to note that no single genetic abnormality by itself defines high-risk MM. It is important to determine the presence or absence of a panel of cytogenetic abnormalities to properly identify patients with an adverse prognosis [33]. Gene expression profiling (GEP) is an alternative method that combines the influence of multiple genetic abnormalities and pathways into a single signature. Although GEP could be a potential method for risk assessment in MM, methods to define a standardized user-friendly GEP signature are required for its widespread use [33].

2. Emerging novel biomarkers

When diagnosing and staging multiple myeloma (MM), markers such as plasma cell percentage [34], β2 microglobulin, albumin [35], and Bence Jones proteins[36] are commonly used only a few cases. However, newer markers and liquid biopsy[37] offer a non-invasive approach to detecting the disease. Certain extracellular matrix (ECM) proteins which are also known as angiogenesis markers, such as laminins, nidogens, and fabulous, show promise as markers for diagnosis, prognosis, or therapeutics in MM [38, 39]. Circulatory tumor cells (CTCs), miRNAs, and cell-free DNA (cfDNA) can help predict disease status, determine minimal residual disease (MRD), and improve prognostic accuracy [40]. The use of liquid biopsy for the evaluation of plasma cells, nucleic acids (such as cell free DNA and microRNAs) is a promising and non-invasive approach for efficiently detecting MM. Liquid biopsy can serve as a reliable indicator of BM, making it a user-friendly and advancing technique.

Immunotherapy using immune-modulating drugs (IMIDs) like lenalidomide or pomalidomide is followed by monoclonal antibodies such as daratumumab and elotuzumab, which have been approved for treating relapsed cases of MM [40]. Proteomics analysis in MM patients has revealed dysregulated expression of certain proteins such as amyloid A protein, vitamin D-binding protein isoform-1 [41], proteasome activator complex subunit 1 (PSME1), PSME2, heat shock protein 90 [42] that could potentially serve as markers for diagnosis or prognosis prediction. Liquid biopsy offers a non-invasive way to comprehensively investigate the disease's molecular profile in the peripheral circulation, providing all relevant information about the disease and its response to treatment [43].

Discussion

Multiple myeloma (MM) is a challenging cancer that affects plasma cells in the bone marrow. MM is the second most common type of blood cancer after non-Hodgkin lymphoma, ranging from a benign condition known as monoclonal gammopathy of unknown significance (MGUS) to a more serious form called plasma cell leukemia [44]. However, through the International Myeloma Working Group's updated criteria for therapy initiation, clinicians and researchers are encouraged to make a difference in the lives of those affected by this disease. While diagnosing MM can be problematic, the potential for a non-invasive liquid biopsy approach using novel biomarkers offers hope. These biomarkers provide valuable information about the disease and its response to treatment, Additionally, it can assist in evaluating MRD to predict the probability of relapse in MM [45]. As diagnostic and therapeutic biomarkers continue to be developed, researchers and clinicians alike can be inspired by the ongoing studies that aim to better understand MM. By working together, we can continue to make progress in the fight against this disease, bringing hope to those affected by it.

References

1. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, (2002) et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. 346(8):564-569.
2. Mateos M-V, San Miguel J-FJTNEJoM. (2013) Treatment for high-risk smoldering myeloma. 369(18):1764-1765.
3. haematology IMWGJBjo. (2003) Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. 121(5):749-757.
4. Dispenzieri A, Gertz MA, Therneau TM, Kyle RA, editors. (2001) Retrospective cohort study of 148 patients with polyclonal gammopathy. Mayo Clinic Proceedings, Elsevier.
5. Kazandjian D, Mailankody S, Korde N, Landgren OJCAHO. (2014) Smoldering multiple myeloma: pathophysiologic insights, novel diagnostics, clinical risk models, and treatment strategies. 12(9):578-587.
6. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, et al. (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. 15(12): e538-e48.
7. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. (2014) Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. 28(5):1122-1128.
8. Walker BA, Wardell CP, Johnson DC, Kaiser MF, Begum DB, et al. (2013) Characterization of IGH locus breakpoints in multiple myeloma indicates a subset of translocations appear to occur in pregerminal center B cells. 121(17):3413-9.
9. Pratt GJMP. (2002) Molecular aspects of multiple myeloma. 55(5):273.
10. Bergsagel PL, Kuehl WMJJoco. (2005) Molecular pathogenesis and a consequent classification of multiple myeloma. 23(26):6333-6338.
11. Murase T, Ri M, Narita T, Fujii K, Masaki A, Iida S, et al. (2019) Immunohistochemistry for identification of CCND1, NSD2, and MAF gene rearrangements in plasma cell myeloma. 110(8):2600-2606.
12. Binder M, Rajkumar S, Ketterling R, Greipp P, Dispenzieri A, Lacy M, et al. (2017) Prognostic implications of abnormalities of chromosome 13 and the presence of multiple cytogenetic high-risk abnormalities in newly diagnosed multiple myeloma. 7(9): e600-e.
13. Bolli N, Maura F, Minvielle S, Gloznik D, Szalat R, Fullam A, et al. (2018) Genomic patterns of progression in smoldering multiple myeloma. 9(1):3363.
14. Furukawa Y, Kikuchi JJIjoh. (2016) Epigenetic mechanisms of cell adhesion-mediated drug resistance in multiple myeloma. 104:281-292.
15. Hari PN, Zhang M-J, Roy V, Pérez WS, Bashey A, To LB, et al. (2009) Is the international staging system superior to the Durie–Salmon staging system? A comparison in multiple myeloma patients undergoing autologous transplant. 23(8):1528-1534.
16. Rajkumar SVJASoCOEB. (2016) Updated diagnostic criteria and staging system for multiple myeloma. 36: e418-e23.
17. Durie BG, Salmon SEJC. (1975) A clinical staging system for multiple myeloma correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. 36(3):842-854.
18. Greipp PR, Miguel JS, Durie BG, Crowley JJ, Barlogie B, et al. (2005) International staging system for multiple myeloma. 23(15):3412-3420.

19. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. (2015) Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. 33(26):2863.
20. Tandon N, Rajkumar S, LaPlant B, Pettinger A, Lacy M, et al. (2017) Clinical utility of the Revised International Staging System in unselected patients with newly diagnosed and relapsed multiple myeloma. 7(2): e528-e.
21. Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, (2001) The Journal of the American Society of Hematology. Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. 97(9):2900-2902.
22. Zamagni E, Cavo M, Fakhri B, Vij R, (2018) Roodman DJASoCOEB. Bones in multiple myeloma: imaging and therapy. 38:638-646.
23. Kishimoto RK, Freitas SLVVd, Ratis CA, Borri D, Sitnik R, (2016) Velloso EDRPJRbdheh. Validation of interphase fluorescence in situ hybridization (iFISH) for multiple myeloma using CD138 positive cells. 38:113-120.
24. Shaughnessy Jr J, Zhan F, Barlogie B, Stewart AJBP, (2005) Haematology RC. Gene expression profiling and multiple myeloma. 18(4):537-552.
25. Ferraro R, Agarwal A, Martin-Macintosh EL, Peller PJ, Subramaniam RMJR. (2015) MR imaging and PET/CT in diagnosis and management of multiple myeloma. 35(2):438-454.
26. Al Saleh AS, Parmar HV, Visram A, Muchtar E, Buadi FK, Go RS, et al. (2020) Increased bone marrow plasma-cell percentage predicts outcomes in newly diagnosed multiple myeloma patients. 20(9):596-601.
27. Tiselius AJTotFS. (1937) A new apparatus for electrophoretic analysis of colloidal mixtures. 33:524-531.
28. Tiselius A, Kabat EAJTJoem. (1939) An electrophoretic study of immune sera and purified antibody preparations. 69(1):119.
29. Korngold L, Lipari RJC. (1956) Multiple-myeloma proteins. III. The antigenic relationship of Bence Jones proteins to normal gamma-globulin and multiple-myeloma serum proteins. 9(2):262-272.
30. Mead G, Carr-Smith H, Drayson M, Morgan G, Child J, Bradwell AJBjoh. (2004) Serum free light chains for monitoring multiple myeloma. 126(3):348-354.
31. Larsen J, Kumar S, Dispenzieri A, Kyle R, Katzmann J, Rajkumar SJL. (2013) Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. 27(4):941-946.
32. Munshi NC, Anderson KC, Bergsagel PL, Shaughnessy J, Palumbo A, Durie B, et al. (2011) Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. 117(18):4696-700.
33. Levin A, Hari P, Dhakal BJTR. (2018) Novel biomarkers in multiple myeloma. 201:49-59.
34. Willrich MA, Katzmann JAJCC, Medicine L. (2016) Laboratory testing requirements for diagnosis and follow-up of multiple myeloma and related plasma cell dyscrasias. 54(6):907-19.
35. Bethea M, Forman DJAoC, Science L. (1990) Beta 2-microglobulin: its significance and clinical usefulness. 20(3):163-8.
36. Delman G, Gally JJTJoem. (1962) The nature of Bence-Jones proteins: chemical similarities to polypeptide chains of myeloma globulins and normal γ-globulins. 116(2):207-227.
37. Crowley E, Di Nicolantonio F, Loupakis F, Bardelli AJNrCo. (2013) Liquid biopsy: monitoring cancer-genetics in the blood. 10(8):472-484.
38. Ashkenas J, Muschler J, Bissell MJJDb. (1996) The extracellular matrix in epithelial biology: shared molecules and common themes in distant phyla. 180(2).
39. Dziadek MJE. (1995) Role of laminin-nidogen complexes in basement membrane formation during embryonic development. 51:901-913.
40. Gupta N, Sharma A, Sharma AJCca. (2020) Emerging biomarkers in multiple myeloma: a review. 503:45-53.
41. Zhang H-T, Tian E-B, Chen Y-L, Deng H-T, Wang Q-TJCmj. (2015) Proteomic analysis for finding serum pathogenic factors and potential biomarkers in multiple myeloma.128(08):1108-1113.
42. Łuczak M, Kubicki T, Rzetelska Z, Szczepaniak T, Przybyłowicz-Chalecka A, Ratajczak B, et al. (2017) Comparative proteomic profiling of sera from patients with refractory multiple myeloma reveals potential biomarkers predicting response to bortezomib-based therapy. 127(6):392-400.
43. Ferreira B, Caetano J, Barahona F, Lopes R, Carneiro E, et al. (2020) Liquid biopsies for multiple myeloma in a time of precision medicine. 98:513-525.
44. Rajkumar SV, Kumar S, editors. (2016) Multiple myeloma: diagnosis and treatment. Mayo Clinic Proceedings; Elsevier.
45. Pantel K, Alix-Panabières CJNRCO. (2019) Liquid biopsy and minimal residual disease—latest advances and implications for cure. 16(7):409-424.

DOI:10.31579/2640-1053/170